The Effect of Enhanced External Counterpulsation Therapy and Improvement of Functional Capacity in Chronic Heart Failure patients: a Randomized Clinical Trial

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ABSTRAK

Tujuan: *untuk mengevaluasi efektivitas terapi enhanced external counterpulsation (EECP) dalam memperbaiki kapasitas fungsional pasien gagal jantung kronik (GJK).* ***Metode:*** *uji klinik acak tersamar ganda dilakukan terhadap 99 pasien GJK yang menjalani terapi EECP di Klinik Jantung Jade, Manado pada periode waktu Januari 2014-Juni 2015. Pasien dibagi menjadi 2 kelompok dimana 49 pasien mendapatkan terapi sham EECP dan 50 pasien mendapatkan terapi EECP. Semua pasien GJK dilakukan latihan jalan 6 menit (LJ6M) sebelum dan sesudah menjalani terapi EECP.* ***Hasil:*** *karakterisitik dasar pasien GJK tidak ditemukan adanya perbedaaan bermakna antara kedua kelompok. Hasil LJ6M sebelum terapi pada kelompok sham EECP ditemukan 30 pasien (61,2%) dengan jarak tempuh <300 meter sedangkan pada kelompok yang dilakukan terapi EECP sebesar 34 pasien (68%), p=0,24. Pasca terapi EECP ditemukan 33 pasien (67,3%) dengan jarak tempuh <300 meter pada kelompok sham EECP, sedangkan pada kelompok terapi EECP hanya 1 pasien (2%), p<0,01. Jarak tempuh pada kelompok sham sebelum terapi adalah 252,65 (SD 97,55) meter dan pada kelompok EECP 243,65 (SD 86,96) meter; p=0,18. Pada kelompok EECP jarak tempuh LJ6M sebelum dilakukan terapi adalah sebesar 256,88 (SD 85,56) meter dan sesudah terapi EECP jarak tempuhnya menjadi sebesar 449,46 (SD 92,08) meter; p<0,01.* ***Kesimpulan:*** *terapi EECP efektif dalam memperbaiki kapasitas fungsional pada pasien GJK.*

Kata kunci: *gagal jantung kronis, latihan jalan 6 menit, terapi enhanced external counterpulsation.*

ABSTRACT

Aim: *to investigate the efficacy of enhanced external counterpulsation (EECP) therapy to improve functional capacity in patients with chronic heart failure (CHF).* ***Methods:*** *a double-blind random clinical trial was performed in 99 patients with CHF who had received EECP therapy at Jade Cardiovascular Clinic, Manado, North Sulawesi, Indonesia between January 2014 and June 2015. Subjects were categorized into 2 groups, i.e. 49 subjects had sham EECP therapy and 50 subjects had EECP therapy. All subjects performed six-minute walking test (6MWT) before and after receiving EECP therapy.* ***Results:*** *there was no significant difference between both groups regarding the basic characteristics of patients with CHF. The 6MWT result before EECP therapy showed that there were 30 patients (61.2%) with walk distance of <300 meter in the sham EECP group; while*

in the group receiving EECP therapy, we found 34 patients (68%); p=0.24. Post-EECP therapy, there were 33 patients (67.3%) with walk distance of <300 meters in EECP sham group; while in the group receiving EECP alone, there was only 1 patient (2%); p <0.01.The 6MWT walk distance in sham group before EECP therapy was 252.65 (SD 97.55) meters and it was 243.65 (SD 86.96) meters following the EECP therapy; p=0.18. In EECP group, the 6MWT walk distance before therapy was 256.88 (SD 85.56) meters and after EECP therapy the walk distance was 449.46 (SD 92.08) meters; p<0.01. ***Conclusion:*** *EECP therapy is effective to improve functional capacity in patients with CHF.*

Key words: *chronic heart failure, six-minute walk test, enhanced external counterpulsation (EECP) therapy.*

INTRODUCTION

Heart failure is still a major health problem. The incidence of heart failure is increasing from 1.5-4% to 6.7-9.9% in developing countries.[1-3] In patients with chronic heart failure (CHF), there is a reduced left ventricular ejection fraction (LVEF), cardiomegaly, and increased left ventricular end diastolic pressure (LVEDP), which will produce clinical manifestations such as short of breath (dyspnea), fatigue, insomnia, easily awake due to shortness of breath that result in limited daily physical activity and impair the functional capacity of patients.[3-6]

In patients with CHF, functional capacity is a method to evaluate patient's ability to perform daily activity, which can be measured by performing six-minute walking test (6MWT). The 6MWT is a simple test, which is easily performed and it is usually utilized to evaluate functional exercise capacity, walking capacity and the effectiveness of treatment in patients with CHF.[4-9]

Various treatment methods have been performed to increase survival and improve quality of life for patients with chronic heart disease. One of those various methods that have been applied recently in the last decade is enhanced external counterpulsation (EECP) therapy. The therapy is used to improve contractility of myocardium and increase stroke volume in addition to its angiogenesis and atherogenesis effect as well as developing new collateral circulation. Enhanced external counterpulsation is a treatment of choice for patients with CHF who still have symptoms of fatigue after receiving optimal pharmacological treatment and for those who are not eligible for having revascularization treatment.[10-14]

Some studies show that EECP treatment does not provide significant improvement effect on increased left ventricular ejection fraction or on exercise tolerance; however, some studies on the effects of EECP therapy have recently provided evidence about its beneficial effect for patients with angina pectoris and heart failure.[10-12,15-17] However, there is very limited data about EECP studies on chronic heart failure. The 6MWT was performed to evaluate their functional capacity. Our study was aimed to evaluate the effectiveness of EECP treatment to improve functional capacity in patients with CHF.

METHODS

Our study was designed to evaluate functional capacity using six-minute walking test in patients with CHF, on those who had received EECP therapy or who only had sham EECP therapy. The study was conducted at the Jade Cardiovascular Clinic, Manado, North Sulawesi, Indonesia between January 2014 and June 2015. The target population in our study was all patients with chronic heart failure; while the study population was patients with chronic heart failure who had treatment at the Jade Cardiovascular Clinic, Manado Siloam Hospital, Manado Adventist Hospital and Prof. Dr. R.D. Kandou General Hospital, Manado. The subjects of our study were all patients with CHF who were eligible as well as those who had met the inclusion criteria and who were willing to participate in our study.

The inclusion criteria of our study were patients with: 1) age between 25 and 79 years; 2) mild to moderate symptomatic chronic heart failure (NYHA functional class I-II) with the following etiology: ischemic heart disease, hypertension heart disease, coronary heart

disease or acute coronary syndrome; 3) certain echocardiography result, i.e. the difference between end diastolic volume and end systolic volume divided with end diastolic volume was <40%; 4) chronic heart disease who had received standard therapy according to the heart failure national guideline for at least one month before participating in our study; 5) willingness to participate in the study and signed the informed consent form.

The exclusion criteria were those with:[11,15,16] 1) severe heart valve damage; 2) acute coronary syndrome at least <6 weeks prior to the study; 3) major arrhythmia that significantly can interfere the EECP instrument such as atrial fibrillation, extra systole of more than six times per minute; 4) heart catheterization <2 weeks prior to the study; 5) history of bypass surgery <3 months and history of coronary stent implant less than 6 months prior to the study and peripartum cardiomyopathy; 6) implantable cardioverter defibrillator instrument; 7) pregnancy and breastfeeding; 8) intermittent claudication; 9) uncontrolled blood pressure of >180/110 mmHg; 10) deep vein thrombosis, thrombophlebitis, pulmonary embolism or aortic aneurysm; 11) other medical, legal or social condition that may affect the patients' judgment in giving their informed consent or when participating the study. The drop out criteria were patients who did not complete EECP/Sham EECP therapy either with or without reason including those who had cardiovascular or severe side effect as well as those who had lost their interest in our study.

Intervention

The EECP instrument consists of 3 pairs of pneumatic cuff, which were applied to lower extremities. The patients were treated for 1 hour daily for a total of 36 sessions in 7 weeks. Three sets of pneumatic cuff were applied to calves, lower and upper thigh and were sequentially inflated during the diastolic phase of the heart. Furthermore, an external pressure of 300 mmHg was applied during the diastolic phase for subjects in EECP therapy group; while those in sham EECP group only had 75 mmHg, enough to preserve the appearance and feel of an EECP application, but insufficient to alter measurably the patient's blood pressure. All patients then performed the six-minute walking test. The test was conducted as indoor test in a straight corridor which had 30 meters length as recommended by the American Thoracic Society (ATS) guideline.

Sample Size

Number of needed samples was calculated using statistical formula based on the difference of walking distance in six minutes between patients with and without EECP intervention. Confidence interval of 95% and statistical power of 80% were applied in the sample size calculation. Based on our previous clinical experience, the estimated Standard Deviation of walking distance was 90 meters and the minimal expected significant difference between both groups after intervention was 50 meters, thus the needed sample size is 50 subjects for each group.

There were 158 patients who had received optimal medical treatment were included in our study and after having screening test, 46 patients were excluded as 15 patients were not willing to participate in our study and 31 patients did not meet the inclusion criteria. The patients subsequently underwent further tests and filled the form about basic characteristics data for population study such as demography, risk factors for coronary heart disease, laboratory data on blood glucose and cholesterol level as well as echocardiography and medication.

Randomization and Blind

Our study was a double blind randomized clinical trial, in which the evaluator did not know about the category of subject groups. We did not know whether the patients with CHF were in the group receiving EECP or sham EECP therapy. Block randomization using concealed envelopes was then performed and the subjects were categorized into 2 groups, i.e. there were 56 patients in the sham EECP group and other 56 patients in the EECP therapy group. The study participants were recruited by the participating cardiologists following the study protocol. The test was carried out by 2 specific clinical nurses at the Jade Cardiovascular Clinic. During the treatment period, 7 patients were excluded from the sham EECP group; consisted of 4 patients that were dropped out since they could not complete the study, and 3 patients had cardiovascular

adverse events (rehospitalized); while in the EECP group, we found 6 patients who were not able to continue the study including 3 dropped out patients, 1 patient who had lost his interest to continue the study and 2 patients who had cardiovascular events (rehospitalized). There were 49 patients who completed EECP treatment in sham group and there were 50 patients in EECP group. Afterwards, all patients performed the six-minute walking test.

Statistical Analysis

Statistical analysis was performed for all outcomes including primary, secondary and safety outcomes. Data were processed using mean value (standard deviation) and were tested with unpaired mean difference (median). In order to evaluate the difference between EECP and sham EECP data, unpaired student T-test was used when the data in both groups showed normal distribution; when it did not show normal distribution, a Mann-Whitney ranks test was used. Alpha of 5% was used in interpreting statistical significance. The data of our study was analyzed using a computer software program of SPSS version 22.0.

Study Protocol

Patients with CHF who were in stable condition of NYHA functional class I and II and who had received optimal treatment for coronary heart disease, including beta blocker, nitrate, aspirin and statin performed six-minute walking test and filled in the WHO-5 questionnaires. They were then randomly selected to receive EECP treatment or non-EECP treatment (i.e. only receiving optimal sham therapy to imitate EECP treatment). An evaluation was subsequently conducted in 6 weeks following the EECP treatment, both for EECP and sham EECP group by performing the six-minute walking test.

Our study was conducted in keeping with Helsinki declaration and was supported by ethical clearance. The ethical clearance was issued by ethic committee of Faculty of Medicine, University of Sam Ratulangi, Manado with registration number 014.01.06/11.2/018/2014. All patients were obliged to sign informed consent before participating in our study.

RESULTS

The study was conducted between January 2014 and June 2015. **Figure 1** shows a flow chart for participants in the study. Outcome measures of 6MWT were collected at baseline and after EECP therapy.

Based on the results of our study, we found that most of CHF patients in both groups were male and they were most frequently at the age of 55-65 years. From the basic characteristic data of patients, we did not find significant difference between those in EECP group and those in sham EECP group as presented in **Table 1**.

Table 2 shows that there was no significant difference of pre-treatment six-minute walking test results between sham EECP and EECP group either for walking distance of <300 meters

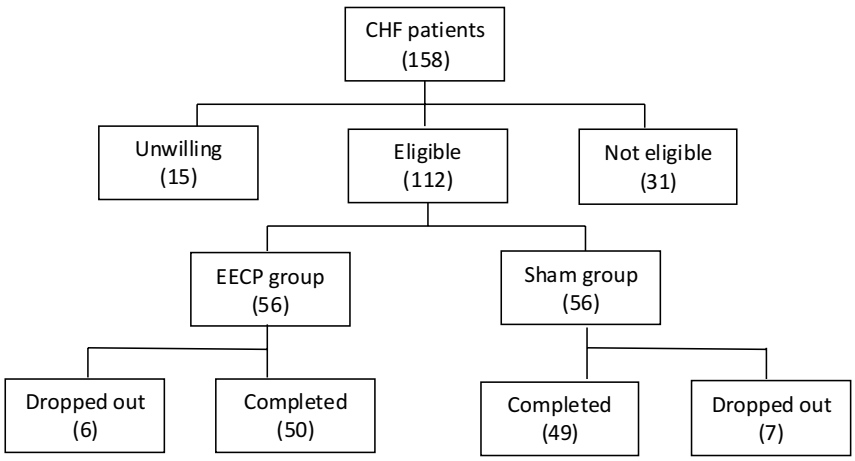

Figure 1. The participants' flow diagram

Table 1. Descriptive baseline characteristics of the study population

Characteristics	Pre Sham Group (n= 49)	Pre EECP Group (n= 50)
Demographic		
Age (year),mean (SD)	62.43 (12.06)	60.54 (8.6)
Gender (male), n (%)	38 (77.6)	36 (72.0)
Weight (kg),mean (SD)	61.8 (11.74)	58.5 (12.02)
Height (cm),mean (SD)	162,6 (8.92)	160.4 (8.69)
BMI (kg/m^2),mean (SD)	23.67 (3.48)	23.06 (4.10)
Cardiovascular Risk factor		
Dyslipidemia, n (%)	34 (69.4)	34 (68.0)
Hypertension, n (%)	35 (70.1)	35 (71.4)
Smoking, n (%)	16 (32.7)	20 (49.0)
Diabetes mellitus,n (%)	13 (26.5)	14 (28.0)
Family predisposition, n (%)	14 (28.6)	8 (16.0)
Blood Parameters		
Fasting glucose (mg/dL), mean (SD)	109.41 (42.52)	95.54 (32.60)
HbA1c, n (%)	6.83 (1.81)	6.18 (2.05)
Total cholesterol (mg/dL), mean (SD)	218.33 (74.16)	210.08 (49.61)
LDL cholesterol (mg/dL), mean (SD)	160.12 (33.94)	157.86 (49.16)
HDL cholesterol (mg/dL), mean (SD)	33.76 (8.46)	38.50 (8.18)
Triglycerides (mg/dL), mean (SD)	134.59 (82.84)	133.06 (71.09)
Echocardiography findings		
LVEDD (mm),mean (SD)	61.89 (9.18)	63.54 (8.66)
LVESD (mm),mean (SD)	50.47 (8.65)	51.96 (8.14)
LVEF (%), mean (SD)	32.69 (3.82)	31.88 (3.95)
Medications		
Aspirin, n (%)	48 (97.9)	48 (96.0)
Statin, n (%)	48 (97.9)	49 (98.0)
β-blocker, n (%)	40 (81.6)	41 (82.0)
Ace Inhibitors/ARB, n (%)	44 (89.8)	45 (90.0)
Nitrates, n (%)	41 (83.7)	43 (86.0)
Exercise tolerance 6 MWT (m), mean (SD)	252.65 (97.55)	256.88 (85.56)

LVEDD = Left ventricular end diastolic diameter; LVESD = Left ventricular end-systolic diameters;LVEF = Left ventricular ejection fraction; LDL = Low density lipoprotein

(61.2% vs. 68.0%) or for walk distance of >300 meters (38.8% vs. 32.0%); p=0.24. **Table 2** also shows results on post-six-minute walking test and we found significant increased walking

Table 2. Comparison of 6 MWT distance between Sham EECP group and EECP group before and after EECP therapy

Variables	6 MWT Distance		ρ value
	≤300 m	>300 m	
Before Intervention, n (%)			
- Sham group (n=49)	30 (61.2)	19 (38.8)	0.24*
- EECP group (n=50)	34 (68.0)	16 (32.0)	
After Intervention, n (%)			
- Sham group (n=49)	33 (67.3)	16 (32.7)	<0.01*
- EECP group (n=50)	1 (2.0)	49 (98.0)	

*Chi square test

distance in EECP group in which 98% subjects had significant statistical rate for walk distance of >300 meters (p<0.01); while in sham EECP group, we found no significant difference when compared to pre-EECP treatment.

There was no significant difference of the six-minute walking test results in the sham EECP group between before and after treatment (252.65 [SD 97.55] vs. 243.65 [SD 86.96]; p=0.18). However, there was a significant increased result of six-minute walking test in EECP group (256.88 [SD 85.56] vs. 449.46 [SD 92.08]; p<0.01) as we can see in **Table 3**. Delta analysis after and before EECP of both group also shows significantly different (-9 [SD 67.68] vs 192.58 [SD 87.45]; p<0.05).

DISCUSSION

The mechanism of action for EECP in alleviating symptoms of chronic angina has not been fully understood; however, the hemodynamic effect of EECP is basically the same with intra-aortic balloon pump (IABP), i.e. by reducing afterload and increasing coronary perfusion pressure through diastolic pressure in aortic root. At the initial phase of left ventricular diastolic, the sets of pneumatic cuff were subsequently inflated and applied to the calves, upper and lower thigh-one at a time. The inflated cuffs will cause arterial and venous compression of the lower extremities and pump the blood to superior part of the body, both to the aortic root

Table 3. Comparison of 6 MWT distance between Sham EECP group and EECP group before and after EECP therapy

Variables	Before	After	Δ Analysis after - before
6 MWT distance, mean (SD)			
Sham group	252.65 (97.55)	243.65 (86.96)	-9 (67.68)
EECP group	256.88 (85.56)	449.46 (92.08)	192.58 (87.45)*

*Mann Whitney Rank test; # p<0.01

and cava vein. The blood pumping may produce increased aortic diastolic pressure, which may push strong and oxygen-rich blood toward the heart and increasing the perfusion pressure of coronary artery.[11,12]

In chronic heart failure, reduced vascular shear stress occurs persistently, which may worsen endothelial dysfunction. The EECP will produce pulsatile blood circulation, which will increase Endothelial shear stress (ESS) leading to improved endothelial function, reduced pro-inflammatory cytokines, lower macrophage accumulation and complement activation and reduced vascular inflammation.[17] In general, the mechanism of action of EECP is to reduce afterload and lower myocardial oxygen demand. EECP increases coronary blood flow and promotes myocardial collateralization through the development of collateral blood vessels, arteriogenesis and angiogenesis. Increased blood flow and ESS can improve endothelial function, vasodilatation and myocardial perfusion.[11]

Recently, there are studies about EECP therapy in patients with heart failure, which demonstrate that the therapy is beneficial in improving exercise capacity, quality of life and functional status with a small number of side effects. A study by Michaels et al evaluated the advantages of EECP on aortic, intracoronary and left ventricular hemodynamic with left heart catheterization. The study concludes that EECP has the same effect with IABP. EECP has also been known as a procedure to increase venous return and contributes to increased cardiac output without any increase in heart rate. Michael et al found that increased preload during EECP has a balance effect on reduced afterload, which gives neutral effect on myocardial efficiency.[18] Masuda et al[19] demonstrate that EECP may induce the release of angiogenesis factors. ANP and BNP levels were found lower after EECP therapy and NO (nitrite oxide) level was higher during rest. Masuda et al[19] show that there is improved coronary vasodilatation and myocardial perfusion following the EECP therapy. The PEECH (Prospective Evaluation of EECP in Heart Failure) study in patients with heart failure (class II and III NYHA classification) indicate that EECP therapy can increase exercise duration, improve NYHA functional status and quality of life.[16] Results of "MUST-EECP" (Multicenter Study of Enhanced External Counterpulsation) show that EECP therapy is safe and effective for patients with chronic heart failure.[20]

In our study, six-minute walking test performed in all patients after they completed the EECP/ sham EECP treatment. The six-minute walking test is an indicator and predictor for health and physical ability status. According to the American Thoracic Society (ATS), six-minute walking test is able to measure various capacity level, such as the capacity of cardiovascular and respiratory system, hemodynamic changes, systemic and peripheral circulation as well as neuromuscular metabolism.[21]

The six-minute walking test in our study showed high significance difference (**Table 2 and 3**) between EECP group and sham EECP group at the end of our observation ($p<0.01$). The increased walking distance of six-minute test found in patients who had received routine EECP therapy indicates that there is increased functional capacity. Improved functional capacity post-EECP is associated with a significant and persistent increase of exercise capacity through increased oxygen uptake, increased tolerance and better exercise duration.[11,15,22] In our study, there were 49 patients (98%) who could have >300 m walking distance following the EECP therapy

compared to those in sham EECP group (32.7%) as seen in **Table 2**. EECP therapy is similar to a physical exercise and gives effects as if we are running since it increases blood flow and shear stress of arterial muscular layer in the lower extremities. Continuous movement will increase NO release from endothelial cells and produce vasodilatation. Increased NO release in coronary artery during EECP therapy has been correlated to improve reservoir of coronary blood flow and endothelial function associated with increased myocardial perfusion and exercise tolerance. Another study has also demonstrated that EECP therapy increases NO release to improve peripheral endothelial function and vaso-relaxation of the smooth muscle.[23] Improved endothelial function is associated with improved heart function and symptoms experienced by the patient.[24]

Increased walking distance in six-minute walking test (>300 m) in EECP group indicates improved functional capacity in patients with heart failure. This result has been proved in our study as seen in **Table 3**. There is improvement of walking distance in EECP group compare with sham group. It was shown that there is a significant difference of delta analysis after and before EECP between two groups. A study by O'Connor et al[25] for patients with chronic heart failure who also underwent six-minute walking test also demonstrated a great improvement of walking distance after physical exercise in 3-month observation. A number of patients demonstrated peak increase of oxygen uptake.[25,26] Improved functional capacity as shown by increased walking distance of six-minute walking test is a beneficial EECP effect and it contributes to lower cardiovascular incidence, less recurrent hospitalization and lower mortality rate of patients with CHF.

This study has limitation due to the fact that some of participants from both groups had to be dropped out of the study. However, despite its limitation, the findings of this study could be generalized for CHF patients with NYHA class I-II that can be improved their functional capacity using EECP treatment.

CONCLUSION

EECP therapy is safe and effective. It brings beneficial effects on improved quality of life in patients with chronic heart failure as demonstrated by increased walking distance in six-minute walking test.

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